

What is the impact of mass and systematic antibiotic administration on antibiotic resistance in low- and middle-income countries? A systematic review

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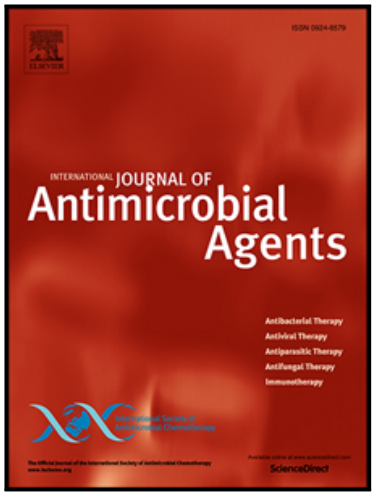
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Highlights:

- Mass and systematic antibiotic administration target a large portion of communities
- These interventions may increase the level of antibiotic resistance
- Particularly after azithromycin and co-trimoxazole administration
- More systematic and standardized surveillance of resistance is urgently needed

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Title page

Title What is the impact of mass and systematic antibiotic administration on antibiotic resistance in low- and middle-income countries? A systematic review

Running Title: AR after mass/systematic antibiotic administration

Authors

Lison Rambliere[1,2], Didier Guillemot[1,2,3], Elisabeth Delarocque-Astagneau[1,3], Bich-Tram Huynh[1,2]

Affiliations

1- Université Paris-Saclay, UVSQ, Inserm, CESP, Anti-infective evasion and pharmacoepidemiology team, F- 78180, Montigny-Le-Bretonneux, France

2- Institut Pasteur, Epidemiology and Modelling of Antibiotic Evasion (EMAE), F-75015, Paris, France

3- AP-HP. Paris Saclay, Public Health, Medical Information, Clinical research, F-94276, Le Kremlin-Bicêtre

Key words

Antibiotic resistance, prophylaxis, mass drug administration, systematic drug administration, Antibiotic usage, global health, Public health, low- and middle-income countries

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Lison Ramblière (corresponding author)

Address: 25-28 rue du Dr Roux, 75015 Paris

Telephone: +33 (0)1 45 68 83 01

Fax: 01 45 68 82 04

E-mail: lison.rambliere@pasteur.fr

Abstract

Antibiotic consumption is a key driver of antibiotic resistance (AR), particularly in low- and middle-income countries, where risk factors for AR emergence and spread are rife. However, the potential contribution of mass and systematic antibiotic administration (MDA/SDA) to AR spread is unknown. We conducted a systematic review to provide an overview of MDA/SDA in low- and middle-income countries, including indications, antibiotics used and, if investigated, levels of AR over time. This systematic review is reported in accordance with the PRISMA statement. Of 2438 identified articles, 63 were reviewed: indications for MDA/SDA were various, and targeted populations were particularly vulnerable, including pregnant women, children, HIV-infected populations and communities in outbreak settings. Available data suggest MDA/SDA may lead to significant AR increase, especially after azithromycin administration. However, only 40% of studies evaluated AR. Integrative approaches that evaluate AR in addition to clinical outcomes are needed to understand consequences of MDA/SDA implementation, combined with standardized AR surveillance for timely detection of antibiotic resistance emergence.

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Units and Abbreviatons:

AR: Antibiotic Resistance

MDA: Mass Drug Administration

SDA: Systematic Drug Adminitration

LMICs: Low- and Middle-income countries

Introduction

Antibiotic resistance (AR) is one of the greatest threats to global health, particularly in low- and middle-income countries (LMICs) where risk factors for its emergence are widespread. Bacterial infections are already leading causes of death in LMICs, and further dissemination of AR could lead to increased mortality due to treatment failure, particularly in settings with restricted access to second-line drugs *[1]*.

Poor infection control, inadequate sanitation and poor living conditions have been identified as key drivers of AR in LMICs. Misuse, over-the-counter availability and low quality of antibiotics are also important contributors to AR in these settings *[2]*. Though antibiotics are predominantly used for treatment of bacterial infections, they are also used for prophylaxis at both the individual and population levels. Mass prophylactic use of antibiotics can broadly be classified as either mass drug administration (MDA) or systematic drug administration (SDA). MDA describes administration of antibiotics to entire communities to control the spread of particular infectious diseases. For instance, WHO (World Health Organization) recommends azithromycin MDA for trachoma control in high-prevalence settings *[3]*. Systematic drug administration (SDA) aims to prevent specific health outcomes or complications by prescribing antibiotics to targeted groups.

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For example, co-trimoxazole can be given to HIV-infected individuals to prevent opportunistic infections *[4]*. Both of these repeated individual and/or large population exposures to antibiotics may play a critical role in the emergence and spread of AR *[5–7]*.

To our knowledge no systematic review has been conducted to describe antibiotic MDA/SDA interventions, despite their significance to public health and potentially important consequences for AR. The main objectives of this study were (i) to provide a descriptive overview of MDA/SDA interventions implemented in LMICs, including indications, targeted populations, antibiotics used and modes of administration, and (ii) to investigate their potential impact on AR.

Methods

We systematically reviewed the literature for studies describing use of MDA/SDA in LMICs. This systematic review is reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement (Supplementary Table 1). The full study protocol was registered with PROSPERO, number CRD42020140182.

Search strategy and selection criteria

PubMed, Web of Science, Scopus and Cochrane Library were searched for articles published between January 2000 and January 2019. Additional searches were conducted monthly until March 2020 to capture recently published literature. Further information was obtained using snowball searching by screening references identified from articles.

We used comprehensive Boolean search strategies with search terms pertaining to antibiotics, MDA, SDA and corresponding English MeSH headings for each database (Supplementary Text 1).

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Articles included were original research articles describing antibiotic MDA or SDA interventions, with indication of administration that could potentially targeted a substantial part of the population in at least one countries defined as LMICs by the World Bank *[8]* (2019). Exclusion criteria were systematic reviews and meta-analyses articles (only used as a source of references in snowball searches), data collection prior to January 1 2000 and studies on MDA for trachoma control, owing to a recently updated systematic review and meta-analysis investigating AR following azithromycin MDA for trachoma control *[9]*. No language restrictions were applied.

Three researchers were involved in the review process (LR, BTH and EDA). One reviewer (LR) assessed article titles for relevance. Two of the three investigators (LR and BTH or EDA) independently reviewed all potentially relevant abstracts. The same process was used for full text screening and quality assessment. Disagreements were resolved by consensus among all parties.

For all eligible studies, we extracted details on objectives, methods and MDA/SDA characteristics. If AR was evaluated, epidemiological and microbiological methods were extracted. We stratified studies by target populations and types of antibiotic, and summarized data on AR when evaluated (resistant pathogen prevalence, measures of association).

The Critical Appraisal Skills Programme tools based on Cochrane guidelines were used to assess study quality. To assess data extraction quality, two investigators (LR and BTH or EDA) reviewed extracted data for selected articles.

Findings

Overall, 2438 articles were identified (Figure 1). After duplicate removal, 2131 articles were eligible for title screening, of which 150 were eligible for abstract screening. Of 86 full-text

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articles assessed, 63 met our inclusion criteria. These 63 articles described 36 different studies across 19 countries. The majority of studies were from Africa (32 studies, 89%), in particular Southern Africa (17 studies, 47%) (Figure 2). Twenty-five studies (69%) were randomized controlled trials and 26 (72%) were implemented in an urban setting. Other study characteristics are available in supplementary Table 2.

Antibiotics administered

Overall, the most commonly used antibiotic was co-trimoxazole (16 studies, 14 of which among HIV-exposed or –infected individuals), with dosing consistent with international recommendations. Other common antibiotics under study were azithromycin (seven studies) and amoxicillin (six studies), with variable dosing. Details of populations, antibiotic, doses and frequency, and main outcomes investigated are presented in Table 1 and Figure 3.

Populations Targeted

Fourteen of the 36 studies (39%) assessed MDA/SDA in children *[10–40]*.

MDA was administered to healthy infants in three studies *[10–22]*. First, ARMCA investigated the impact of amoxicillin, co-trimoxazole or azithromycin MDA on infant weight gain *[10–12]*. Second, MORDOR assessed the effect of azithromycin MDA on infant morbidity and mortality *[13–21]*. The last study investigated the effect on infant morbidity and mortality of adding azithromycin to seasonal malaria chemoprophylaxis *[22]*.

Five studies targeted severely malnourished infants under two years old *[23–27]*. Among them, four investigated the impact of amoxicillin as SDA on nutritional recovery *[23–26]*, of which two further included arms with ceftriaxone *[24]* or cefdinir *[25]*. The fifth assessed the impact of co-trimoxazole as SDA on mortality *[27]*.

Six studies targeted HIV-exposed or -infected children *[28–40]*, all in the context of co-trimoxazole as SDA to decrease morbi-mortality.

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Eleven studies [41–59] (31%) evaluated efficacy of SDA in pregnant women.

Six studies targeted healthy pregnant women [41–53], of which four evaluated azithromycin to decrease maternal/infant morbidity, preterm birth or low birth weight, or to improve gestational weight gain [42–51]. Two studies evaluated antibiotic SDA to prevent early neonatal sepsis, using either amoxicillin, cephalexin or penicillin [41], or ampicillin in combination or not with metronidazole [53].

Three studies targeted HIV-infected pregnant women [54–57] to prevent morbi-mortality using either co-trimoxazole [57], cefoxitin [56], or metronidazole in combination with erythromycin or ampicillin [54,55].

The remaining two studies targeted women with risk factors at delivery [58,59]. The first administered ampicillin to women with premature rupture of fetal membranes to prevent early onset neonatal sepsis [58]. The other assessed cefazolin administration at cord clamping to prevent maternal infections among women who underwent Caesarian section [59].

Eight studies (22%) investigated co-trimoxazole as SDA in HIV-infected adults [60–68] (or adults and children) and its potential to decrease mortality rates, infections or malaria incidence.

The remaining three studies (8%) described MDA in outbreak settings [69–72] which administered : doxycycline to contacts of cholera patients in Cameroon [69]; ciprofloxacin to members of Nigerien villages with high prevalence of meningitis [70]; and azithromycin to members of villages with high prevalence of yaws in Papua New Guinea [71,72].

Antibiotic resistance

AR was evaluated post-baseline (after first antibiotic administration) in 39% of studies [11,17,18,32,36,37,39,50,52,60,63,66–72] (14/36): in 36% (5/14) of studies among children

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[11,17,18,32,36,37,39], in 18% (2/11) among pregnant women [50,52], in 50% (4/8) among HIV-infected adults [60,63,66–68], and in 100% (3/3) in outbreak settings [69–72]. Of note, two additional studies investigated AR at baseline without post-exposure follow-up and were thus excluded from the following results [23,48]. AR was detected with either phenotypic [17,32,36,37,50,52,60,63,66–70] (11/14) or molecular methods [11,17,18,39,71,72] (4/14) with one study using both methods [17].

Four studies with both intervention and control groups evaluated carriage of resistant bacteria cross-sectionally *[11,17,18,36,60]* (table 2). Single sampling time points ranged from 6 to 730 days following first antibiotic administration. AR was evaluated longitudinally in ten studies [32,36,37,39,50,52,60,63,66–72] (Figure 4). Follow-up ranged from 30 days to ten years.

Azithromycin

Of seven studies investigating azithromycin MDA/SDA, four evaluated AR.

Two studies, both among healthy children, investigated gut meta-genomic resistance after MDA. In ARMCA, antibiotic resistance determinants corresponding to each antibiotic class were identified using DNA-seq extracted from rectal swabs [11]. Five days after last MDA, increases in prevalence of macrolide and sulfonamide resistance genes were found (RR=3.6, $p<0.001$ and RR=16.0, $p=0.01$) [11]. For resistance genes for other antibiotic classes, such as beta-lactams and fluoroquinolones, prevalence was not different between antibiotic and placebo groups [11]. In MORDOR, antibiotic resistance determinants/genes identified were Ls, ermA, ermB, ermF, ermT, ermX, lnuA, lnuC, Lsa, macB, mefA, MEL, mphA, msrD [18]. Six months after last MDA, determinants of macrolide resistance from metagenomic DNA sequencing were significantly higher in the antibiotic group than in placebo in the intestinal flora (12.3% vs. 2.9%, $p= 0.02$) and in the nasopharyngeal flora (68.8% vs. 46.7%, $p=0.002$) [17]. The presence of genetic resistance determinants at the DNA level is not always associated with phenotypic

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resistance. This requires analysis of gene expression at the RNA level. In MORDOR, the expression of macrolide resistance genes in the gut was also significantly higher in the antibiotic group than in the placebo group (16.7% vs. 2.7%, p=0.001 [18]).

Two studies, one in infants (MORDOR) [17] and the other in pregnant women [50], assessed *Streptococcus pneumoniae* resistance. In MORDOR, the proportion of resistance to erythromycin in nasopharyngeal samples was higher in the antibiotic group than controls (12.3% vs. 2.9%, p=0.02) [17]. In pregnant women receiving antibiotics, proportions of *S. pneumoniae* and *S. aureus* resistant to azithromycin were higher compared to the control group in nasopharyngeal, breast milk and vaginal samples at day 28 [50]. While antibiotics were administered only to mothers, infants born to mothers in the antibiotic group had higher rates of *S. aureus* resistant to azithromycin in nasopharyngeal samples taken at one month of age (4.5% vs 16.7%, p<0.001), but rates were similar to controls at 12 months (3.1% vs. 2.6%, p=0.724) [50,52]. Prevalence of resistant *S. pneumoniae* and *S. aureus* to other antibiotic classes (such as erythromycin, chloramphenicol, and clindamycin) was similar between both arms at 28 days and 12 months [52].

In a study evaluating *Treponema pallidum* resistance after azithromycin MDA in residents of yaws-endemic villages [71,72], rates of macrolide resistance genes (*A2058G* and *A2059G*) did not change over time and remained below 10% [71] (Supplementary Figure 1).

Co-trimoxazole

Of the sixteen studies in which co-trimoxazole was used as SDA, nine evaluated AR.

AR was assessed using meta-genomic analysis in two studies. Analysis of rectal swabs from healthy infants from ARMCA showed a significant increase in risk of carrying sulfonamide (RR=8.8, p=0.05) and trimethoprim (RR=3.3, p=0.04) resistance gene determinants relative to the placebo group, while no difference was observed for beta-lactam and macrolide resistance

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genes [11]. The second study targeted HIV-exposed uninfected infants [39]. In the group treated with co-trimoxazole compared to placebo, the authors showed a decrease of gut microbiome β-diversity (diversity in resistance gene composition), increased AR gene α-diversity (resistance gene richness) (p=0.0045) and increased overall resistance gene prevalence (p=0.007) [39].

S. pneumoniae AR was investigated in three studies [32,36,68]. Based on a national surveillance system, Everett and colleagues reported a high rate of co-trimoxazole resistance (>90%) in *S. pneumoniae* cultures of cerebrospinal fluid and blood from adults and children admitted to hospital for severe bacterial infection [68]. No resistance to other antibiotics such as tetracycline, chloramphenicol or penicillin was reported [68]. The two remaining studies investigated AR in nasopharyngeal samples of HIV-infected children: high levels of co-trimoxazole resistance were observed at baseline in both antibiotic (85.2% [36] and 58% [32]) and control groups (83.3% [36] and 60% [32]), with an increase in both groups observed in the first months of administration [36]. Over two years, one study showed a higher level of co-trimoxazole resistant *S. pneumoniae* in the co-trimoxazole arm than in the placebo arm (88%/72% $p < 0.0001$) [32]. The proportion of *Haemophilus influenzae* resistant to co-trimoxazole was also higher in the co-trimoxazole arm [32]. The second study found an increase in nasopharyngeal colonization with *S. pneumoniae* resistant to co-trimoxazole (RR=3.2, p=0.04) and clindamycin (RR=1.6, p=0.04) [36]. However, no increase was detected for resistance to penicillin, erythromycin, tetracycline or chloramphenicol [36].

Four studies investigated phenotypic AR of fecal *Escherichia coli*: all in HIV-infected or -exposed populations.

In adults, proportions of *E. coli* resistant to co-trimoxazole were similar at 24 weeks in both groups. In the co-trimoxazole arm compared to placebo higher proportions of *E. coli* resistant to ampicillin (OR=10.2, p<0.001), chloramphenicol (0R=7.8, p<0.001), ciprofloxacin (OR=17.1,

p=0.006) and nalidixic acid (OR=26.4, p=0.001) were found [60]. In HIV-exposed but uninfected infants, the proportion of *E. coli* resistant to co-trimoxazole was higher in co-trimoxazole recipients compared with placebo (3 months: 94% vs. 51% p<0.0001, 6 months: 84% vs. 57% p=0.01); as well as in *Klebsiella spp.* at 3 months (94% vs. 51% p<0.0001) and 6 months (69% vs. 14% p=0.002)[37]. In HIV-infected patients with CD4-cell counts <350 cell/mm3, the resistant rate of *E. coli* to co-trimoxazole was 54% (29% in the control group) and reached 100% (53%) at 12 months [63]. Resistance rates were also higher when compared to baseline for ampicillin (from 74% to 100%), amoxicillin/clavulanic acid (from 33% to 100%) and ceftriaxone (from 2% to 54%) [63]. In the remaining study, 76% of bacterial isolates (*E. coli*, *Shigella spp.*, *Campylobacter spp.* or *Salmonella spp.*) were classified as resistant before, and 83% after co-trimoxazole use among HIV-infected adults [67]. In their HIV-negative family members with diarrhea, no difference in the proportion of resistance to co-trimoxazole was observed [66].

Amoxicillin

Of the five studies using amoxicillin as MDA, AR was evaluated in only one study [11]. While prevalence of beta-lactam, macrolide and trimethoprim resistance genes were not significantly different, prevalence of sulfonamide resistance was higher in the amoxicillin arms compared to control (RR=15.3, p=0.01) [11].

Ciprofloxacin

Fecal carriage of extended-spectrum beta-lactamase producing *Enterobacteriaceae* was evaluated in a cluster-randomized trial evaluating administration of a single oral dose of ciprofloxacin to prevent meningococcal meningitis [70]. Carriage of ciprofloxacin-resistant *Enterobacteriaceae* was higher than 90% at baseline and at 28 days post-intervention without significant change observed (Supplementary Figure 1) [70].

Doxycycline

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Doxycycline was administered to contacts of cholera patients and *Vibrio cholerae* resistance was tested in stool samples of cholera patients during the eight months of outbreak [69]. The authors reported stable susceptibility patterns, including high rates of resistance for co-trimoxazole and colistin, and low rates for amoxicillin, clavulanic acid, cefotaxime, doxycycline, and perfloxacin [69].

Discussion

MDA/SDA interventions can reduce the burden of infectious diseases and improve population health [73–75]. Yet MDA/SDA may also contribute to the mounting global health crisis posed by AR [5–7]. We conducted an exhaustive review of published MDA/SDA studies conducted in LMICs since 2000 and, when evaluated, their impacts on AR.

We found that MDA/SDA interventions targeted a diverse range of particularly vulnerable populations, including severely malnourished infants, pregnant women, young children, HIV-exposed and -infected individuals, and communities in outbreak settings. These populations are over-represented in many LMICs [76–79] and sometimes overlap, such that the same individuals may be targeted by more than one MDA/SDA. Three main families of antibiotics were administered for three main purposes: amoxicillin and azithromycin administration for weight gain, ampicillin to prevent neonatal sepsis, and co-trimoxazole to decrease mortality and morbidity. Despite potentially important consequences for AR, only 14 of 36 included studies (40%) evaluated AR following MDA/SDA. However limited, our findings are consistent with the expectation that MDA/SDA interventions lead to greater AR prevalence, especially after co-trimoxazole and azithromycin administration. Co-trimoxazole resistance was high at baseline in *E. coli* [37,60,63,66,67](>50%) and *S. pneumoniae* [36,68] (>75%), yet increased further in

several populations receiving co-trimoxazole MDA/SDA. In some included studies, co-trimoxazole prophylaxis was followed by increased resistance to other antibiotic classes such as aminopenicillins, chloramphenicols and quinolones [60]. It is possible that co-trimoxazole induces cross-resistance, although there is currently no scientific consensus [80]. One alternative explanation is that co-trimoxazole resistance genes can be found alongside other resistance genes, for example on the same plasmid [80]. Another explanation for co-trimoxazole favouring resistance to unrelated antibiotics, such as clindamycin, is co-selection of related antibiotic resistance genes [80].

Azithromycin MDA/SDA was associated with increased macrolide resistance in *S. pneumoniae*, *S. aureus* [50,52,81], and increased resistance genes among microbiota [11,17,18]. These results are concordant with those reported by O'brien *et al.* that found a transient or persistent increase in the proportion of *S. pneumoniae*, *E. coli* and *S. aureus* resistant to macrolides after MDA for trachoma control [9].

MDA/SDA is currently recommended by WHO for various indications, so potentially large numbers of people are eligible recipients. For example, following recent updates to treatment guidelines, WHO now recommends SDA for children with uncomplicated severe acute malnutrition, both in hospital and community settings, without practical guideline such as antibiotic class, dose or duration [82].

Since 2014, in settings with high infectious disease prevalence, WHO also recommends co-trimoxazole for all HIV-infected persons, irrespective of their CD4 count, as well as HIV-exposed neonates until 6 weeks of age [4]. With HIV prevalence above 20% in some LMICs [78], significant proportions of the population may be eligible for SDA under these guidelines.

Guidelines for other uses of MDA/SDA will likely evolve as more evidence from current and future studies becomes available. This has potential to further expand populations targeted by

these interventions. For instance, a research priority identified by WHO is evaluation of SDA for all women during the second or third trimesters of pregnancy to prevent infectious morbidity [83]. Several randomized controlled trials investigating azithromycin MDA are currently ongoing, targeting diverse populations including children after discharge from hospital, children with non-severe diarrhoea and malnourished children [84–86]. Moreover, in several low-income countries the official guidelines for treatment of Covid-19 patients at the primary care level recommend azithromycin for mild symptomatic Covid-19 patients, asymptomatic contacts or for prophylaxis [87].

The vast majority of included studies were set in Africa, thus limiting information regarding the indications and populations targeted by MDA/SDA and their potential impact on AR in others continents.

Epidemiological methods were heterogeneous without systematic evaluation of AR over time. AR can be transient [88–90] or may remain elevated for long periods because of low fitness costs of resistance [91] and/or continued selection pressure from other sources of antibiotic consumption. Temporal dynamics of AR were often poorly described or difficult to interpret, largely owing to variability in study design and duration of follow-up, which varied from five days to ten years.

Most studies investigated AR only in the treatment group, and evaluated AR only to the focal antibiotic and among few bacterial species. In addition, AR was evaluated only in bacteria specifically targeted by MDA/SDA, yet antibiotic exposure broadly selects for resistance across human microflora, particularly in the digestive tract [7,92]. In addition to the focal pathogen, assessment of resistance across non-focal species and across multiple antibiotic classes will be necessary to assess the overall impact of broad-spectrum antibiotic use on pathogenic bacterial species. AR is a concern not only for individuals targeted by MDA/SDA, but also their contacts

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and environments, raising concerns about propagation of multidrug-resistant bacteria both within individuals and throughout communities. For example, among pregnant women receiving azithromycin MDA, rise of AR in *S. aureus* was also observed in their untreated neonates [50]. Better understanding of mechanisms of AR across species could help to better target particular bacteria while minimizing bystander selection [75]. Microbiological assessment of AR was also highly heterogeneous, and included phenotypic, molecular or metagenomic testing methods. Phenotypic methods can identify resistance of specific organisms to specific antibiotics, and are commonly used to characterize AR among both gram-positive and gram-negative bacteria. Metagenomic methods can detect resistance determinants in several types of organisms at the same time, but cannot determine whether this affects pathogenic or non-pathogenic bacteria. These complementary methods should be considered simultaneously for future cross-assessments. Moreover, the microbiome can be affected in terms of bacterial abundance, richness and diversity [5]. It may take long periods for microbiota to recover and return to a species composition similar to baseline, particularly in the context of repeated administration during vulnerable time periods, such as childhood [5,7]. Disruption of the microbiome can further select for emergence of resistant pathogens responsible for acute disease and increase risk of intestinal infection [5]. More studies are needed to better understand potentially far-reaching consequences of MDA/SDA on the microbiome.

To our knowledge, this review is the first to provide a global overview of MDA/SDA administration and its potential impact on AR. Our findings suggest that MDA/SDA with antibiotics such as azithromycin and co-trimoxazole may lead to significant increases in AR levels across bacterial species. Guidelines for AR evaluation in the context of MDA/SDA are sorely needed, including integrative approaches that incorporate standardized methodologies for AR evaluation.

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Declarations

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References

[1] Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J-A, Klugman K, et al. Access to effective antimicrobials: a worldwide challenge. Lancet 2016;387:168–175. doi:10.1016/S0140-6736(15)00474-2.

[2] Morgan DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg S. Non-prescription antimicrobial use worldwide: a systematic review. Lancet Infect Dis 2011;11:692–701. doi:10.1016/S1473-3099(11)70054-8.

[3] A guide for programme managers n.d.

[4] www.who.int/hiv/pub/guidelines/arv2013/December2014-ARVsupplement-chap8.pdf n.d.

Journal Pre-proof

[5] Francino MP. Antibiotics and the Human Gut Microbiome: Dysbioses and Accumulation of Resistances. Front Microbiol 2015;6:1543. doi:10.3389/fmicb.2015.01543.

[6] Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. Clin Infect Dis 2008;46:155–164. doi:10.1086/524891.

[7] Mack I, Sharland M, Berkley JA, Klein N, Malhotra-Kumar S, Bielicki J. Antimicrobial resistance following azithromycin mass drug administration: potential surveillance strategies to assess public health impact. Clin Infect Dis 2020;70:1501–1508. doi:10.1093/cid/ciz893.

[8] World Bank Country and Lending Groups – World Bank Data Help Desk n.d. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups (accessed April 17, 2020).

[9] O'Brien KS, Emerson P, Hooper PJ, Reingold AL, Dennis EG, Keenan JD, et al. Antimicrobial resistance following mass azithromycin distribution for trachoma: a systematic review. Lancet Infect Dis 2019;19:e14–e25. doi:10.1016/S1473-3099(18)30444-4.

[10] Oldenburg CE, Sié A, Coulibaly B, Ouermi L, Dah C, Tapsoba C, et al. Effect of commonly used pediatric antibiotics on gut microbial diversity in preschool children in burkina faso: A randomized clinical trial. Open Forum Infect Dis 2018;5:ofy289. doi:10.1093/ofid/ofy289.

[11] Oldenburg CE, Hinterwirth A, Sié A, Coulibaly B, Ouermi L, Dah C, et al. Gut resistome after oral antibiotics in preschool children in Burkina Faso: A randomized controlled trial. Clin Infect Dis 2019. doi:10.1093/cid/ciz455.

Journal Pre-proof

[12] Sié A, Dah C, Ouermi L, Tapsoba C, Zabre P, Bärnighausen T, et al. Effect of Antibiotics on Short-Term Growth among Children in Burkina Faso: A Randomized Trial. Am J Trop Med Hyg 2018;99:789–796. doi:10.4269/ajtmh.18-0342.

[13] Keenan JD, Bailey RL, West SK, Arzika AM, Hart J, Weaver J, et al. Azithromycin to Reduce Childhood Mortality in Sub-Saharan Africa. N Engl J Med 2018;378:1583–1592. doi:10.1056/NEJMoa1715474.

[14] Porco TC, Hart J, Arzika AM, Weaver J, Kalua K, Mrango Z, et al. Mass oral azithromycin for childhood mortality: timing of death after distribution in the MORDOR trial. Clin Infect Dis 2018;68:2114–2116. doi:10.1093/cid/ciy973.

[15] West SK, Bloch E, Weaver J, Munoz B, Mrango Z, Kasubi M, et al. Morbidity in a longitudinal cohort of children residing in villages randomized to 6 monthly treatment with azithromycin versus placebo. Clin Infect Dis 2019. doi:10.1093/cid/ciz269.

[16] Keenan JD, Arzika AM, Maliki R, Boubacar N, Elh Adamou S, Moussa Ali M, et al. Longer-Term Assessment of Azithromycin for Reducing Childhood Mortality in Africa. N Engl J Med 2019;380:2207–2214. doi:10.1056/NEJMoa1817213.

[17] Doan T, Arzika AM, Hinterwirth A, Maliki R, Zhong L, Cummings S, et al. Macrolide Resistance in MORDOR I - A Cluster-Randomized Trial in Niger. N Engl J Med 2019;380:2271–2273. doi:10.1056/NEJMc1901535.

[18] Doan T, Hinterwirth A, Worden L, Arzika AM, Maliki R, Abdou A, et al. Gut microbiome alteration in MORDOR I: a community-randomized trial of mass azithromycin distribution. Nat Med 2019;25:1370–1376. doi:10.1038/s41591-019-0533-0.

[19] Bloch EM, Munoz B, Weaver J, Mrango Z, Lietman TM, West SK. Impact of Biannual Azithromycin on Anemia in Preschool Children in Kilosa District, Tanzania: A Cluster-Randomized Clinical Trial. Am J Trop Med Hyg 2020. doi:10.4269/ajtmh.19-0500.

Journal Pre-proof

[20] Arzika AM, Maliki R, Boubacar N, Kane S, Cook CA, Lebas E, et al. Malaria Parasitemia and Nutritional Status during the Low Transmission Season in the Presence of Azithromycin Distribution among Preschool Children in Niger. Am J Trop Med Hyg 2020. doi:10.4269/ajtmh.19-0547.

[21] Arzika AM, Maliki R, Boubacar N, Kane S, Cotter SY, Lebas E, et al. Biannual mass azithromycin distributions and malaria parasitemia in pre-school children in Niger: A cluster-randomized, placebo-controlled trial. PLoS Med 2019;16:e1002835. doi:10.1371/journal.pmed.1002835.

[22] Chandramohan D, Dicko A, Zongo I, Sagara I, Cairns M, Kuepfer I, et al. Effect of adding azithromycin to seasonal malaria chemoprevention. N Engl J Med 2019;380:2197–2206. doi:10.1056/NEJMoa1811400.

[23] Isanaka S, Langendorf C, Berthé F, Gnegne S, Li N, Ousmane N, et al. Routine amoxicillin for uncomplicated severe acute malnutrition in children. N Engl J Med 2016;374:444–453. doi:10.1056/NEJMoa1507024.

[24] Dubray C, Ibrahim SA, Abdelmutalib M, Guerin PJ, Dantoine F, Belanger F, et al. Treatment of severe malnutrition with 2-day intramuscular ceftriaxone vs 5-day amoxicillin. Ann Trop Paediatr 2008;28:13–22. doi:10.1179/146532808X270635.

[25] Trehan I, Goldbach HS, LaGrone LN, Meuli GJ, Wang RJ, Maleta KM, et al. Antibiotics as part of the management of severe acute malnutrition. N Engl J Med 2013;368:425–435. doi:10.1056/NEJMoa1202851.

[26] Trehan I, Amthor RE, Maleta K, Manary MJ. Evaluation of the routine use of amoxicillin as part of the home-based treatment of severe acute malnutrition. Trop Med Int Health 2010;15:1022–1028. doi:10.1111/j.1365-3156.2010.02580.x.

Journal Pre-proof

[27] Berkley JA, Ngari M, Thitiri J, Mwalekwa L, Timbwa M, Hamid F, et al. Daily co-trimoxazole prophylaxis to prevent mortality in children with complicated severe acute malnutrition: a multicentre, double-blind, randomised placebo-controlled trial. Lancet Glob Health 2016;4:e464–73. doi:10.1016/S2214-109X(16)30096-1.

[28] Prendergast AJ, Bwakura-Dangarembizi M, Mugyenyi P, Lutaakome J, Kekitiinwa A, Thomason MJ, et al. Reduced bacterial skin infections in HIV-infected African children randomized to long-term cotrimoxazole prophylaxis. AIDS 2016;30:2823–2829. doi:10.1097/QAD.0000000000001264.

[29] Chintu C, Bhat GJ, Walker AS, Mulenga V, Sinyinza F, Lishimpi K, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. Lancet 2004;364:1865–1871. doi:10.1016/S0140-6736(04)17442-4.

[30] Walker AS, Mulenga V, Ford D, Kabamba D, Sinyinza F, Kankasa C, et al. The impact of daily cotrimoxazole prophylaxis and antiretroviral therapy on mortality and hospital admissions in HIV-infected Zambian children. Clin Infect Dis 2007;44:1361–1367. doi:10.1086/515396.

[31] Mulenga V, Ford D, Walker AS, Mwenya D, Mwansa J, Sinyinza F, et al. Effect of cotrimoxazole on causes of death, hospital admissions and antibiotic use in HIV-infected children. AIDS 2007;21:77–84. doi:10.1097/QAD.0b013e3280114ed7.

[32] Mwenya DM, Charalambous BM, Phillips PPJ, Mwansa JCL, Batt SL, Nunn AJ, et al. Impact of cotrimoxazole on carriage and antibiotic resistance of Streptococcus pneumoniae and Haemophilus influenzae in HIV-infected children in Zambia. Antimicrob Agents Chemother 2010;54:3756–3762. doi:10.1128/AAC.01409-09.

Journal Pre-proof

[33] Prendergast A, Walker AS, Mulenga V, Chintu C, Gibb DM. Improved growth and anemia in HIV-infected African children taking cotrimoxazole prophylaxis. Clin Infect Dis 2011;52:953–956. doi:10.1093/cid/cir029.

[34] Homsy J, Dorsey G, Arinaitwe E, Wanzira H, Kakuru A, Bigira V, et al. Protective efficacy of prolonged co-trimoxazole prophylaxis in HIV-exposed children up to age 4 years for the prevention of malaria in Uganda: a randomised controlled open-label trial. Lancet Glob Health 2014;2:e727–36. doi:10.1016/S2214-109X(14)70329-8.

[35] Sandison TG, Homsy J, Arinaitwe E, Wanzira H, Kakuru A, Bigira V, et al. Protective efficacy of co-trimoxazole prophylaxis against malaria in HIV exposed children in rural Uganda: a randomised clinical trial. BMJ 2011;342:d1617. doi:10.1136/bmj.d1617.

[36] Gill CJ, Mwanakasale V, Fox MP, Chilengi R, Tembo M, Nsofwa M, et al. Effect of presumptive co-trimoxazole prophylaxis on pneumococcal colonization rates, seroepidemiology and antibiotic resistance in Zambian infants: a longitudinal cohort study. Bull World Health Organ 2008;86:929–938.

[37] Powis KM, Souda S, Lockman S, Ajibola G, Bennett K, Leidner J, et al. Cotrimoxazole prophylaxis was associated with enteric commensal bacterial resistance among HIV-exposed infants in a randomized controlled trial, Botswana. J Int AIDS Soc 2017;20. doi:10.1002/jia2.25021.

[38] Daniels B, Coutsoudis A, Moodley-Govender E, Mulol H, Spooner E, Kiepiela P, et al. Effect of co-trimoxazole prophylaxis on morbidity and mortality of HIV-exposed, HIV-uninfected infants in South Africa: a randomised controlled, non-inferiority trial. Lancet Glob Health 2019;7:e1717–e1727. doi:10.1016/S2214-109X(19)30422-X.

[39] D'Souza AW, Moodley-Govender E, Berla B, Kelkar T, Wang B, Sun X, et al. Cotrimoxazole prophylaxis increases resistance gene prevalence and α-diversity but

Journal Pre-proof

497 decreases β-diversity in the gut microbiome of HIV-exposed, uninfected infants. Clin Infect
498 Dis 2019. doi:10.1093/cid/ciz1186.
499 [40] Bwakura-Dangarembizi M, Kendall L, Bakeera-Kitaka S, Nahirya-Ntege P, Keishanyu R,
500 Nathoo K, et al. A randomized trial of prolonged co-trimoxazole in HIV-infected children
501 in Africa. N Engl J Med 2014;370:41–53. doi:10.1056/NEJMoa1214901.
502 [41] Chan GJ, Stuart EA, Zaman M, Mahmud AA, Baqui AH, Black RE. The effect of
503 intrapartum antibiotics on early-onset neonatal sepsis in Dhaka, Bangladesh: a propensity
504 score matched analysis. BMC Pediatr 2014;14:104. doi:10.1186/1471-2431-14-104.
505 [42] van den Broek NR, White SA, Goodall M, Ntonya C, Kayira E, Kafulafula G, et al. The
506 APPLe study: a randomized, community-based, placebo-controlled trial of azithromycin for
507 the prevention of preterm birth, with meta-analysis. PLoS Med 2009;6:e1000191.
508 doi:10.1371/journal.pmed.1000191.
509 [43] Luntamo M, Kulmala T, Mbewe B, Cheung YB, Maleta K, Ashorn P. Effect of repeated
510 treatment of pregnant women with sulfadoxine-pyrimethamine and azithromycin on
511 preterm delivery in Malawi: a randomized controlled trial. Am J Trop Med Hyg
512 2010;83:1212–1220. doi:10.4269/ajtmh.2010.10-0264.
513 [44] Luntamo M, Kulmala T, Cheung YB, Maleta K, Ashorn P. The effect of antenatal monthly
514 sulphadoxine-pyrimethamine, alone or with azithromycin, on foetal and neonatal growth
515 faltering in Malawi: a randomised controlled trial. Trop Med Int Health 2013;18:386–397.
516 doi:10.1111/tmi.12074.
517 [45] Hallamaa L, Cheung YB, Luntamo M, Ashorn U, Kulmala T, Mangani C, et al. The
518 impact of maternal antenatal treatment with two doses of azithromycin and monthly
519 sulphadoxine-pyrimethamine on child weight, mid-upper arm circumference and head

Journal Pre-proof

circumference: A randomized controlled trial. PLoS One 2019;14:e0216536. doi:10.1371/journal.pone.0216536.

[46] Unger HW, Wangnapi RA, Ome-Kaius M, Boeuf P, Karl S, Mueller I, et al. Azithromycin-containing intermittent preventive treatment in pregnancy affects gestational weight gain, an important predictor of birthweight in Papua New Guinea - an exploratory analysis. Matern Child Nutr 2016;12:699–712. doi:10.1111/mcn.12215.

[47] Unger HW, Ome-Kaius M, Wangnapi RA, Umbers AJ, Hanieh S, Suen CSNLW, et al. Sulphadoxine-pyrimethamine plus azithromycin for the prevention of low birthweight in Papua New Guinea: a randomised controlled trial. BMC Med 2015;13:9. doi:10.1186/s12916-014-0258-3.

[48] Unger HW, Aho C, Ome-Kaius M, Wangnapi RA, Umbers AJ, Jack W, et al. Impact of intermittent preventive treatment in pregnancy with azithromycin-containing regimens on maternal nasopharyngeal carriage and antibiotic sensitivity of Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus: a cross-sectional survey at delivery. J Clin Microbiol 2015;53:1317–1323. doi:10.1128/JCM.03570-14.

[49] Oluwalana C, Camara B, Bottomley C, Goodier S, Bojang A, Kampmann B, et al. Azithromycin in Labor Lowers Clinical Infections in Mothers and Newborns: A Double-Blind Trial. Pediatrics 2017;139. doi:10.1542/peds.2016-2281.

[50] Roca A, Oluwalana C, Bojang A, Camara B, Kampmann B, Bailey R, et al. Oral azithromycin given during labour decreases bacterial carriage in the mothers and their offspring: a double-blind randomized trial. Clin Microbiol Infect 2016;22:565.e1–9. doi:10.1016/j.cmi.2016.03.005.

[51] Roca A, Camara B, Oluwalana C, Lette K, Bottomley C, D'Alessandro U. Long-lasting effect of oral azithromycin taken by women during labour on infant nutrition: Follow-up

Journal Pre-proof

544 cohort of a randomized clinical trial in western Gambia. PLoS One 2018;13:e0206348.
545 doi:10.1371/journal.pone.0206348.
546 [52] Bojang A, Camara B, Jagne Cox I, Oluwalana C, Lette K, Usuf E, et al. Long-term Impact
547 of Oral Azithromycin Taken by Gambian Women During Labor on Prevalence and
548 Antibiotic Susceptibility of Streptococcus pneumoniae and Staphylococcus aureus in Their
549 Infants: Follow-up of a Randomized Clinical Trial. Clin Infect Dis 2018;67:1191–1197.
550 doi:10.1093/cid/ciy254.
551 [53] Schrag SJ, Cutland CL, Zell ER, Kuwanda L, Buchmann EJ, Velaphi SC, et al. Risk
552 factors for neonatal sepsis and perinatal death among infants enrolled in the prevention of
553 perinatal sepsis trial, Soweto, South Africa. Pediatr Infect Dis J 2012;31:821–826.
554 doi:10.1097/INF.0b013e31825c4b5a.
555 [54] Aboud S, Msamanga G, Read JS, Wang L, Mfalila C, Sharma U, et al. Effect of prenatal
556 and perinatal antibiotics on maternal health in Malawi, Tanzania, and Zambia. Int J
557 Gynaecol Obstet 2009;107:202–207. doi:10.1016/j.ijgo.2009.07.037.
558 [55] Kafulafula G, Mwatha A, Chen YQ, Aboud S, Martinson F, Hoffman I, et al. Intrapartum
559 antibiotic exposure and early neonatal, morbidity, and mortality in Africa. Pediatrics
560 2009;124:e137–44. doi:10.1542/peds.2008-1873.
561 [56] Sebitloane HM, Moodley J, Esterhuizen TM. Prophylactic antibiotics for the prevention of
562 postpartum infectious morbidity in women infected with human immunodeficiency virus: a
563 randomized controlled trial. Am J Obstet Gynecol 2008;198:189.e1–6.
564 doi:10.1016/j.ajog.2007.08.053.
565 [57] Nunn AJ, Mwaba PB, Chintu C, Crook AM, Darbyshire JH, Ahmed Y, et al. Randomised,
566 placebo-controlled trial to evaluate co-trimoxazole to reduce mortality and morbidity in

Journal Pre-proof

HIV-infected post-natal women in Zambia (TOPAZ). Trop Med Int Health 2011;16:518–526. doi:10.1111/j.1365-3156.2011.02731.x.

[58] Nabhan AF, Elhelaly A, Elkadi M. Antibiotic prophylaxis in prelabor spontaneous rupture of fetal membranes at or beyond 36 weeks of pregnancy. Int J Gynaecol Obstet 2014;124:59–62. doi:10.1016/j.ijgo.2013.07.018.

[59] Hong F, Zhang L, Zhang Y, Sun W, Hong H, Xu Y. Antibiotic prophylaxis to prevent postoperative infectious morbidity in low-risk elective cesarean deliveries: a prospective randomized clinical trial. J Matern Fetal Neonatal Med 2016;29:1382–1386. doi:10.3109/14767058.2015.1052397.

[60] Morpeth SC, Thielman NM, Ramadhani HO, Hamilton JD, Ostermann J, Kisenge PR, et al. Effect of trimethoprim-sulfamethoxazole prophylaxis on antimicrobial resistance of fecal Escherichia coli in HIV-infected patients in Tanzania. J Acquir Immune Defic Syndr 2008;47:585–591. doi:10.1097/QAI.0b013e31816856db.

[61] Hoffmann CJ, Fielding KL, Charalambous S, Innes C, Chaisson RE, Grant AD, et al. Reducing mortality with cotrimoxazole preventive therapy at initiation of antiretroviral therapy in South Africa. AIDS 2010;24:1709–1716. doi:10.1097/QAD.0b013e32833ac6bc.

[62] Walker AS, Ford D, Gilks CF, Munderi P, Ssali F, Reid A, et al. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. Lancet 2010;375:1278–1286. doi:10.1016/S0140-6736(10)60057-8.

[63] Egwuatu CC, Iwuafor AA, Egwuatu TO, Akujobi CN, Nnachi AU, Aghanya IN, et al. Effect of trimethoprim-sulfamethoxazole prophylaxis on faecal carriage rates of resistant isolates of escherichia coli in hiv-infected adult patients in lagos. Afr J Infect Dis 2016;10:156–163. doi:10.21010/ajid.v10i2.12.

Journal Pre-proof

[64] Polyak CS, Yuhas K, Singa B, Khaemba M, Walson J, Richardson BA, et al. Cotrimoxazole Prophylaxis Discontinuation among Antiretroviral-Treated HIV-1-Infected Adults in Kenya: A Randomized Non-inferiority Trial. PLoS Med 2016;13:e1001934. doi:10.1371/journal.pmed.1001934.

[65] Anywaine Z, Levin J, Kasirye R, Lutaakome JK, Abaasa A, Nunn A, et al. Discontinuing cotrimoxazole preventive therapy in HIV-infected adults who are stable on antiretroviral treatment in Uganda (COSTOP): A randomised placebo controlled trial. PLoS One 2018;13:e0206907. doi:10.1371/journal.pone.0206907.

[66] Mermin J, Lule J, Ekwaru JP, Downing R, Hughes P, Bunnell R, et al. Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members. AIDS 2005;19:1035–1042.

[67] Mermin J, Lule J, Ekwaru JP, Malamba S, Downing R, Ransom R, et al. Effect of co-trimoxazole prophylaxis on morbidity, mortality, CD4-cell count, and viral load in HIV infection in rural Uganda. Lancet 2004;364:1428–1434. doi:10.1016/S0140-6736(04)17225-5.

[68] Everett DB, Mukaka M, Denis B, Gordon SB, Carrol ED, van Oosterhout JJ, et al. Ten years of surveillance for invasive Streptococcus pneumoniae during the era of antiretroviral scale-up and cotrimoxazole prophylaxis in Malawi. PLoS One 2011;6:e17765. doi:10.1371/journal.pone.0017765.

[69] Noeske J, Guévart E, Kuaban C, Solle J, Fonkoua MC, Mouangue A, et al. Routine use of antimicrobial drugs during the 2004 cholera epidemic in Douala, Cameroon. East Afr Med J 2006;83:596–601. doi:10.4314/eamj.v83i11.9475.

[70] Coldiron ME, Assao B, Page A-L, Hitchings MDT, Alcoba G, Ciglenecki I, et al. Single-dose oral ciprofloxacin prophylaxis as a response to a meningococcal meningitis epidemic

Journal Pre-proof

in the African meningitis belt: A 3-arm, open-label, cluster-randomized trial. PLoS Med 2018;15:e1002593. doi:10.1371/journal.pmed.1002593.

[71] Mitjà O, Houinei W, Moses P, Kapa A, Paru R, Hays R, et al. Mass treatment with single-dose azithromycin for yaws. N Engl J Med 2015;372:703–710. doi:10.1056/NEJMoa1408586.

[72] Mitjà O, Godornes C, Houinei W, Kapa A, Paru R, Abel H, et al. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. Lancet 2018;391:1599–1607. doi:10.1016/S0140-6736(18)30204-6.

[73] Lazzerini M, Tickell D. Antibiotics in severely malnourished children: systematic review of efficacy, safety and pharmacokinetics. Bull World Health Organ 2011;89:594–607. doi:10.2471/BLT.10.084715.

[74] Suthar AB, Vitoria MA, Nagata JM, Anglaret X, Mbori-Ngacha D, Sued O, et al. Co-trimoxazole prophylaxis in adults, including pregnant women, with HIV: a systematic review and meta-analysis. Lancet HIV 2015;2:e137–50. doi:10.1016/S2352-3018(15)00005-3.

[75] Oldenburg CE, Arzika AM, Amza A, Gebre T, Kalua K, Mrango Z, et al. Mass Azithromycin Distribution to Prevent Childhood Mortality: A Pooled Analysis of Cluster-Randomized Trials. Am J Trop Med Hyg 2019;100:691–695. doi:10.4269/ajtmh.18-0846.

[76] Malnutrition in Children - UNICEF DATA n.d. https://data.unicef.org/topic/nutrition/malnutrition/#targetText=In%202018%20globally%2C%2049%20million,and%202.4%20per%20cent%2C%20respectively.,%20c%20https://data.worldbank.org/indicator/SH.DYN.AIDS.ZS (accessed April 23, 2020).

[77] Fertility rate, total (births per woman) | Data n.d. https://data.worldbank.org/indicator/SP.DYN.TFRT.IN (accessed April 23, 2020).

Journal Pre-proof

[78] Prevalence of HIV, total (% of population ages 15-49) | Data n.d. https://data.worldbank.org/indicator/SH.DYN.AIDS.ZS (accessed April 23, 2020).

[79] Children (0-14) living with HIV | Data n.d. https://data.worldbank.org/indicator/SH.HIV.0014 (accessed April 23, 2020).

[80] Sibanda EL, Weller IVD, Hakim JG, Cowan FM. Does trimethoprim-sulfamethoxazole prophylaxis for HIV induce bacterial resistance to other antibiotic classes? Results of a systematic review. Clin Infect Dis 2011;52:1184–1194. doi:10.1093/cid/cir067.

[81] Keenan JD, Arzika AM, Maliki R, Elh Adamou S, Ibrahim F, Kiemago M, et al. Cause-specific mortality of children younger than 5 years in communities receiving biannual mass azithromycin treatment in Niger: verbal autopsy results from a cluster-randomised controlled trial. Lancet Glob Health 2020;8:e288–e295. doi:10.1016/S2214-109X(19)30540-6.

[82] WHO | Use of antibiotics in the outpatient management of children 6-59 months of age with severe acute malnutrition n.d. https://www.who.int/elena/titles/antibiotics_sam/en/ (accessed April 23, 2020).

[83] WHO recommendation against routine antibiotic prophylaxis during the second or third trimester to all women with the aim of reducing infectious morbidity | RHL n.d. https://extranet.who.int/rhl/topics/preconception-pregnancy-childbirth-and-postpartum-care/who-recommendation-against-routine-antibiotic-prophylaxis-during-second-or-third-trimester-all-women (accessed April 23, 2020).

[84] Roca A, Oluwalana C, Camara B, Bojang A, Burr S, Davis TME, et al. Prevention of bacterial infections in the newborn by pre-delivery administration of azithromycin: Study protocol of a randomized efficacy trial. BMC Pregnancy Childbirth 2015;15:302. doi:10.1186/s12884-015-0737-3.

Journal Pre-proof

[85] Pavlinac PB, Singa BO, John-Stewart GC, Richardson BA, Brander RL, McGrath CJ, et al. Azithromycin to prevent post-discharge morbidity and mortality in Kenyan children: a protocol for a randomised, double-blind, placebo-controlled trial (the Toto Bora trial). BMJ Open 2017;7:e019170. doi:10.1136/bmjopen-2017-019170.

[86] ABCD study team. A double-blind placebo-controlled trial of azithromycin to reduce mortality and improve growth in high-risk young children with non-bloody diarrhoea in low resource settings: the Antibiotics for Children with Diarrhoea (ABCD) trial protocol. Trials 2020;21:71. doi:10.1186/s13063-019-3829-y.

[87] Chevalier MTM, Moncada SS. Hydroxychloroquine/ chloroquine as a treatment choice or prophylaxis for Covid-19 at the primary care level in developing countries: A Primum non Nocere dilemma. J Neurol Sci 2020;415:116972. doi:10.1016/j.jns.2020.116972.

[88] Andersson DI. Persistence of antibiotic resistant bacteria. Curr Opin Microbiol 2003;6:452–456. doi:10.1016/j.mib.2003.09.001.

[89] Haug S, Lakew T, Habtemariam G, Alemayehu W, Cevallos V, Zhou Z, et al. The decline of pneumococcal resistance after cessation of mass antibiotic distributions for trachoma. Clin Infect Dis 2010;51:571–574. doi:10.1086/655697.

[90] Keenan JD, Chin SA, Amza A, Kadri B, Nassirou B, Cevallos V, et al. The Effect of Antibiotic Selection Pressure on the Nasopharyngeal Macrolide Resistome: A Cluster-randomized Trial. Clin Infect Dis 2018;67:1736–1742. doi:10.1093/cid/ciy339.

[91] Cottell JL, Webber MA, Piddock LJV. Persistence of transferable extended-spectrum-β-lactamase resistance in the absence of antibiotic pressure. Antimicrob Agents Chemother 2012;56:4703–4706. doi:10.1128/AAC.00848-12.

Journal Pre-proof

685 [92] Tedijanto C, Olesen SW, Grad YH, Lipsitch M. Estimating the proportion of bystander
686 selection for antibiotic resistance among potentially pathogenic bacterial flora. Proc Natl
687 Acad Sci USA 2018;115:E11988–E11995. doi:10.1073/pnas.1810840115.
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691 # Table

692

693 **Table 1: Mass or systematic administration of antibiotics among 63 included articles: target populations,**

694 **antibiotics used, antibiotic dosing and frequency, and main outcomes investigated.**

Target population	MDA/SDA[a]	Dose (mg)	Frequency	Main outcomes investigated
Amoxicillin				
1-59m healthy [10–12]	MDA	25/kg	2/d[b] x 5d	Weight gain
1-59m malnourished [23]	SDA	80/kg	2/d x7d	Nutritional recovery
1-59m malnourished [24]	SDA	12.5	1/d x5d	Weight gain
1-59m malnourished [25]	SDA	80/kg	2/d x2w[c]	Mortality and nutritional recovery
6-59m malnourished [26]	SDA	60/kg	1/d x7d	Nutritional recovery
Healthy [41]	SDA	500	1 at delivery	Early-onset neonatal sepsis
Ampicillin				
Vaginal delivery [53]	SDA	1000	1/6h before delivery	Early-onset neonatal sepsis
HIV-infected [54,55]	SDA	500 + 250	3/d x7d	Mortality and morbidity[d]
Pre-labor SROM[e] [58]	SDA	1500	1 at delivery	Early-onset neonatal sepsis
Azithromycin				
1-59m healthy[13–21]	MDA	20/kg	2/y[f] x3y	Mortality, morbidity and resistance gene abundance
1-59m healthy [10–12]	MDA	5/kg	1/d x5d	Mortality, hospital admission
3-59m healthy [22]	MDA	100 or 200	1/d x3d	Weight gain
Healthy [42]	SDA	1000	1 at 2nd and 3rd trimester	Preterm-birth
Healthy [43–45]	SDA	500	2 at 3rd trimester	Preterm deliveries, fetal and neonatal weight
Healthy [29–33]	SDA	500	2/d x2d up to 3 times	Gestational weight gain, birth weight
Healthy [49–52]	SDA	2000	1 at delivery	Mortality and morbidity**, infant weight gain
Yaws outbreak [71,72]	MDA	30/kg	1 dose	Prevalence of yaws
Cefazolin				
C-section [59]	SDA	2000	1 at cord clamping	Maternal infections

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Target population	MDA/SDA[a]	Dose (mg)	Frequency	Main outcomes investigated
Cefdinir				
1-59m malnourished [25]	MDA	14/kg	2/d x2w	Mortality and nutritional recovery
Cefoxitin				
HIV-infected, vaginal delivery [56]	SDA	2000	1 at delivery	Maternal infections
Ceftriaxone				
1-59m malnourished [24]	SDA	50/kg	1/d x5d	Weight gain
Cephalexin				
Healthy [41]	SDA	500	1 at delivery	Early-onset neonatal sepsis
Ciprofloxacin				
Previous meningitis outbreak [70]	MDA	250 or 500	1 dose	Meningitis attack rate
Co-trimoxazole				
1-59m healthy [10–12]	MDA	240	2/d x5d	Weight gain
2-59m malnourished [27]	SDA	120 or 240	1/d x1y	Mortality
3-17y HIV-infected [28,40]	SDA	480 or 960	1/d x96w or x200w	Mortality, hospital admission, skin infection
3-14y HIV-infected [29–33]	SDA	240 or 480	1/d x4y	Mortality, hospital admission, antibiotic consumption and pneumococcal colonization
2-5y HIV-infected [34,35]	SDA	60/kg	1/d x4y	Malaria incidence
0-1y HIV-exposed [36]	SDA	60/kg	1/d x1y	Pneumococcal colonization
0-15m HIV-exposed [37]	SDA	120 or 240	1/d x15m[g]	Colonization of resistant Enterobacteriaceae
0-1y HIV-exposed [38,39]	SDA	120 or 240	1/d	Morbidity and resistance gene abundance
HIV-infected [57]	SDA	480	2/d x16d	Mortality and hospital admission
HIV-infected [60]	SDA	960	2/d	Colonization of resistant *E. coli*
HIV-infected [61]	SDA	960	1/d	Mortality
HIV-infected [62]	SDA	960	1/d	Mortality and malaria incidence
HIV-infected [63]	SDA	960	1/d	Colonization of resistant *E. coli*
HIV-infected with immune recovery [64]	SDA	960	1/d	Mortality and morbidity
HIV-infected with immune recovery [64]	SDA	960	1/d	Incidence of co-trimoxazole-preventable events or death

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Target population	MDA/SDA[a]	Dose (mg)	Frequency	Main outcomes investigated
And children HIV-infected [66,67]	SDA	960	1/d	Mortality and morbidity
>15y HIV-infected [68]	SDA	960	1/d	Pneumococcal colonization
Doxycycline				
contacts of infected Cholera patients [69]	MDA	5/kg	1 dose	Cholera incidence and rate of *V. cholerae* resistance
Erythromicyn				
HIV-infected [54,55]	SDA	500 + 250	3/d x7d	Mortality and morbidity (pregnant women and neonates)
Penicillin				
Healthy [41]	SDA	500	1 at delivery	Early-onset neonatal sepsis

Legends

Infants and children
Pregnant women
HIV-infected individuals
Communities

d- day
w- week
m- month
y- year

a- MDA/SDA: Mass or systematic drug administration
b- d: day
c- w: week
d- of pregnant women and their neonate
e- SROM : Spontaneous Rupture of Membranes
f- y: year
g- m: month

[10–12] – 3 arms : co-trimoxazole, azithromycin, amoxicillin
[41] – 3 arms : amoxicillin, cephalexin, penicillin
[24] – 2 arms : amoxicillin, ceftriaxone
[25] – 2 arms : amoxicillin, cefdinir
[54,55] – 3 arms : ampicillin + metronidazole or erythromycin + metronidazole
[53] – 2 arms : ampicillin or ampicillin + metronidazole

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718 **Table 2: Single time-point evaluation of antibiotic resistance following antibiotic administration**

719 CI-Confidence Interval, MG – metagenomics, PDD - Phenotype disk diffusion, PE- Phenotype ellipsometry

720 1 – Time between first antibiotic administration and sampling, 2 – Control versus intervention, 3- Risk of non-

721 susceptibility when co-trimoxazole non-susceptible

Outcome evaluated	Study name	Sample	Method	Class or antibiotic evaluated	Time[1] (days)	Prevalence exposed / unexposed	Association measure[2]	CI 95%	pvalue
Amoxicillin	ARMCA [11]	Rectal	MG	Beta-lactam	10		3.1	[0.7 ; 13.3]	NS
Resistome	ARMCA [11]	Rectal	MG	Macrolide	10		1.24	[0.6 ; 4.4]	NS
	ARMCA [11]	Rectal	MG	Sulfonamide	10		15.3	[1.8 ; 129.1]	0.01
	ARMCA [11]	Rectal	MG	Trimethoprim	10		1.4	[0.5 ; 4.0]	NS
Azithromycin	MORDOR [18]	Rectal	MG	Aminoglycosides	730	1.3 / 2.7		[0.0 ; 2.7] / [1.0 ; 5.0]	NS
Resistome	MORDOR [17]	Rectal	MG	Aminoglycosides	730	38.0 / 31.3		[29.2 ; 44.7] / [24.7 ; 36.7]	NS
	ARMCA [11]	Rectal	MG	Beta-lactam	10		1.9	[0.5 ; 6.6]	NS
	MORDOR [18]	Rectal	MG	Beta-lactam	730	36.0 / 34.0		[27.3 ; 43.3] / [24.0 ; 44.0]	NS
	MORDOR [17]	Rectal	MG	Beta-lactam	730	68.0 / 63.3		[60.0 ; 74.0] / [56.3 ; 70.7]	NS
	MORDOR [18]	Rectal	MG	Fluoroquinolones	730	4.7 / 2.0		[1.3 ; 9.3] / [0.0 ; 5.0]	NS
	MORDOR [17]	Rectal	MG	Fluoroquinolones	730	27.3 / 28.7		[19.3 ; 35.3] / [22.0 ; 35.3]	NS
	MORDOR [17]	Rectal	MG	Glycopeptides	730	1.3 / 1.3		[0.0 ; 2.7] / [0.0 ; 2.7]	NS
	ARMCA	Rectal	MG	Macrolides	10		2.6	[1.5 ; 4.4]	<0.001

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	[11]								
	MORDOR [18]	Rectal	MG	Macrolides	730	16.7 / 2.7		[9.3 ; 24.7] / [1.0 ; 5.0]	0.001
	MORDOR [17]	Rectal	MG	Macrolides	730	68.0 / 46.7		[61.3 ; 74.0] / [36.0 ; 54.0]	0.002
	MORDOR [18]	Rectal	MG	Metronidazole	730	30.0 / 23.3		[18.7 ; 39.3] / [16.0 ; 30.7]	NS
	MORDOR [17]	Rectal	MG	Metronidazole	730	31.3 / 23.3		[20.7 ; 42.0] / [16.0 ; 29.3]	NS
	ARMCA [11]	Rectal	MG	Sulfonamides	10		16.0	[1.9 ; 133.5]	0.01
	MORDOR [18]	Rectal	MG	Sulfonamides	730	0.7 / 2.0		[0.0 ; 2.0] / [0.0 ; 4.0]	NS
	MORDOR [17]	Rectal	MG	Sulfonamides	730	16.7 / 22.7		[9.3 ; 24.0] / [17.3 ; 29.6]	NS
	MORDOR [17]	Rectal	MG	Tetracyclines	730	75.3 / 74.0		[66.3 ; 80.0] / [68.7 ; 78.7]	NS
	MORDOR [18]	Rectal	MG	Tetracyclines	730	27.3 / 30.7		[20.7 ; 34.7] / [22.7 ; 39.3]	NS
	ARMCA [11]	Rectal	MG	Trimethoprim	10		1.8	[0.7 ; 5.1]	NS
	MORDOR [17]	Rectal	MG	Trimethoprim	730	51.3 / 48.7		[44.0 ; 58.0] / [38.7 ; 57.3]	NS
	MORDOR [18]	Rectal	MG	Trimethoprim	730	2.0 / 2.0		[0.0 ; 4.0] / [0.0 ; 4.0]	NS
Streptococcus	MORDOR [17]	Nasal	PDD	Co-trimoxazole	730	84.7 / 77.1		[76.4 ; 92.4] / [65.4 ; 88.1]	NS
pneumoniae	MORDOR [17]	Nasal	PDD	Clindamycin	730	9.0 / 1.7		[4.3 ; 14.1] / [0.0 ; 4.3]	NS
	MORDOR [17]	Nasal	PDD	Doxycycline	730	60.1 / 50.1		[50.8 ; 70.5] / [33.7 ; 66.0]	NS
	MORDOR [17]	Nasal	PDD	Erythromycin	730	12.3 / 2.9		[5.7 ; 20.0] / [0.0 ; 6.1]	0.02
	MORDOR [17]	Nasal	PDD	Penicillin	730	18.7 / 22.3		[8.2 ; 30.6] / [10.2 ; 37.6]	NS

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Co-trimoxazole	ARMCA [11]	Rectal	MG	Beta-lactam	10	1.8	[0.5 ; 6.4]	NS
Resistome	ARMCA [11]	Rectal	MG	Macrolides	10	8.9	[0.9 ; 3.0]	NS
	ARMCA [11]	Rectal	MG	Sulfonamides	10	8.8	[1 ; 77.0]	0.05
	ARMCA [11]	Rectal	MG	Trimethoprim	10	3.3	[1.1 ; 10.0]	0.04
Escherichia coli	[60]	Rectal	PDD	Ampicillin	7 to 168	10.2[3]	[5.9 ; 17.8]	<0.001
	[60]	Rectal	PDD	Azithromycin	7 to 168	1.2[3]	[0.71 ; 1.9]	NS
	[60]	Rectal	PDD	Chloramphenicol	7 to 168	7.8[3]	[3.0 ; 20.2]	<0.001
	[60]	Rectal	PDD	Ciprofloxacin	7 to 168	17.1[3]	[2.3 ; 127.7]	0.006
Streptococcus pneumoniae	TZI project [36]	Nasal	PE	Chloramphenicol	42	0.8	[0.3 ; 2.3]	NS
	TZI project [36]	Nasal	PE	Clindamycin	42	1.6	[1.0 ; 2.6]	0.04
	TZI project [36]	Nasal	PE	Erythromycin	42	1.0	[0.6 ; 1.7]	NS
	TZI project [36]	Nasal	PE	Penicillin	42	1.1	[0.7 ; 1.7]	NS
	TZI project [36]	Nasal	PE	Tetracycline	42	0.9	[0.6 ; 1.5]	NS

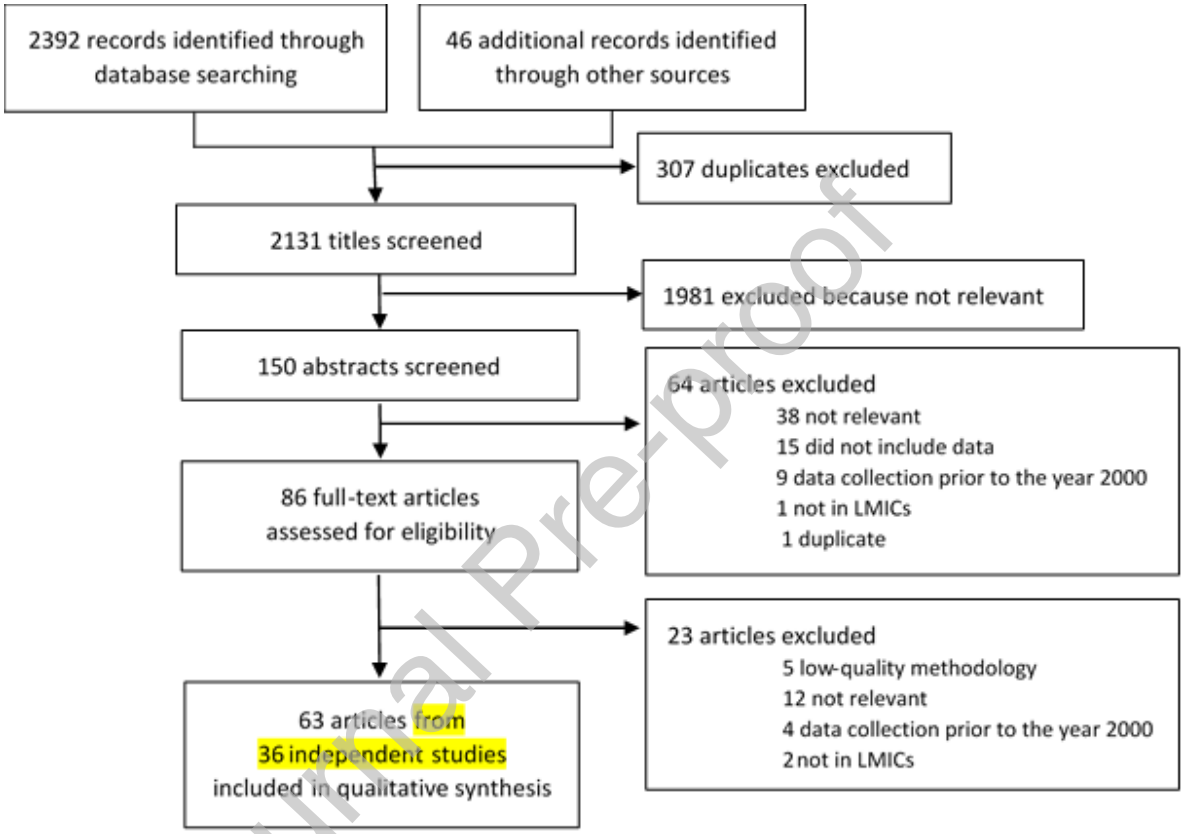
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723 **Figures**

724 **Figure 1 : PRISMA flow diagram**

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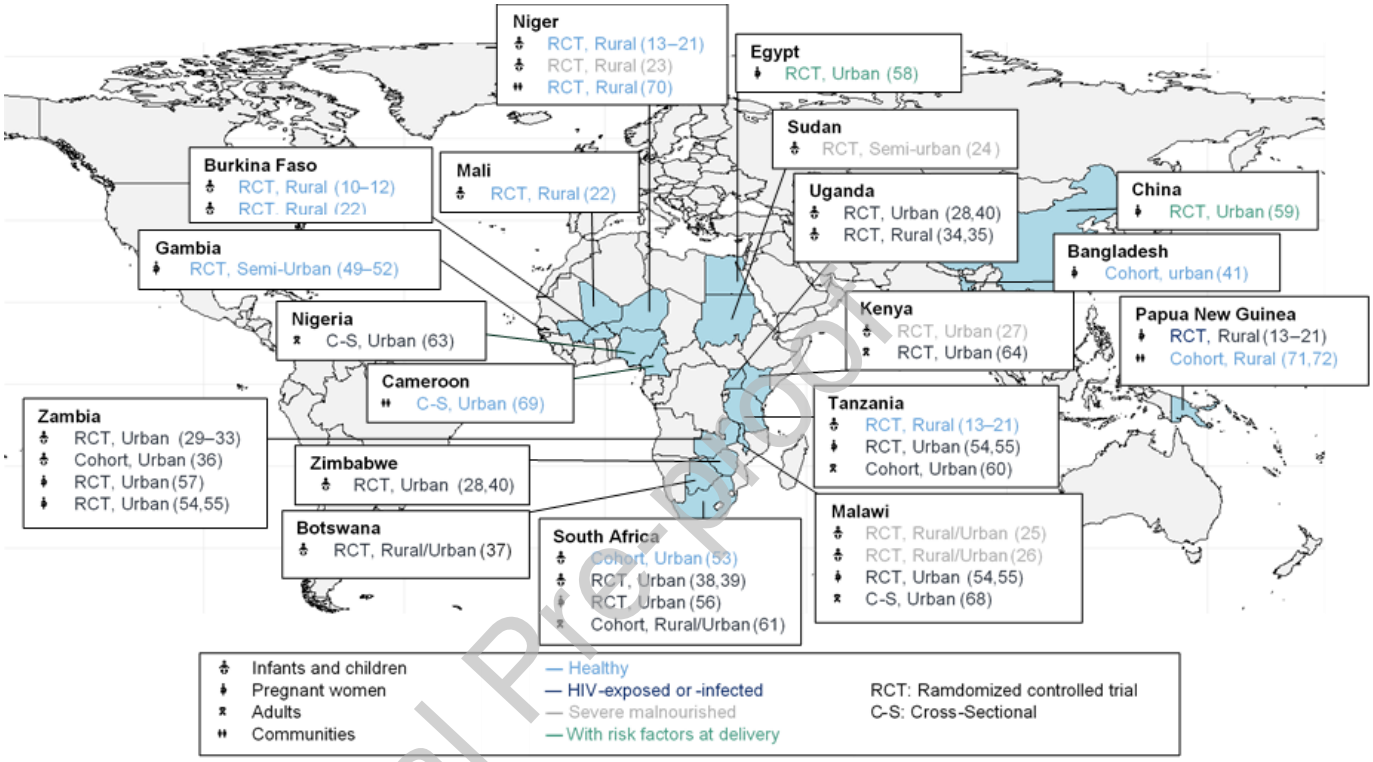


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727 **Figure 2 : Geographic distribution of the 63 included articles (36 studies)**

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731 **Figure 3 : Main populations, antibiotics used and indications for MDA/SDA in LMICs**

	Populations	Antibiotic most commonly used	Intended outcome
 **Childhood**	Healthy infants	azithromycin	↘ mortality
	Malnourished infants	amoxicillin	↗ weight
 **Pregnancy**	Healthy pregnant women	azithromycin	↘ premature delivery ↘ neonatal sepsis ↘ maternal/neonatal mortality ↗ birth weight
	Premature rupture of membranes	ampicillin	↘ Early-onset neonatal sepsis
	C-section	cefazolin	↘ Morbidity
 **HIV**	Infected or exposed pregnant women, infants, children and adults	Co-trimoxazole	↘ morbidity ↘ mortality
 **Outbreak**	Meningitis	Ciprofloxacine	↘ meningitis
	Cholera	Doxycycline	↘ cholera
	Yaws	Azithromycin	↘ yaws

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733 **Figure 4: Longitudinal evaluation of antibiotic resistance with repeated measures**

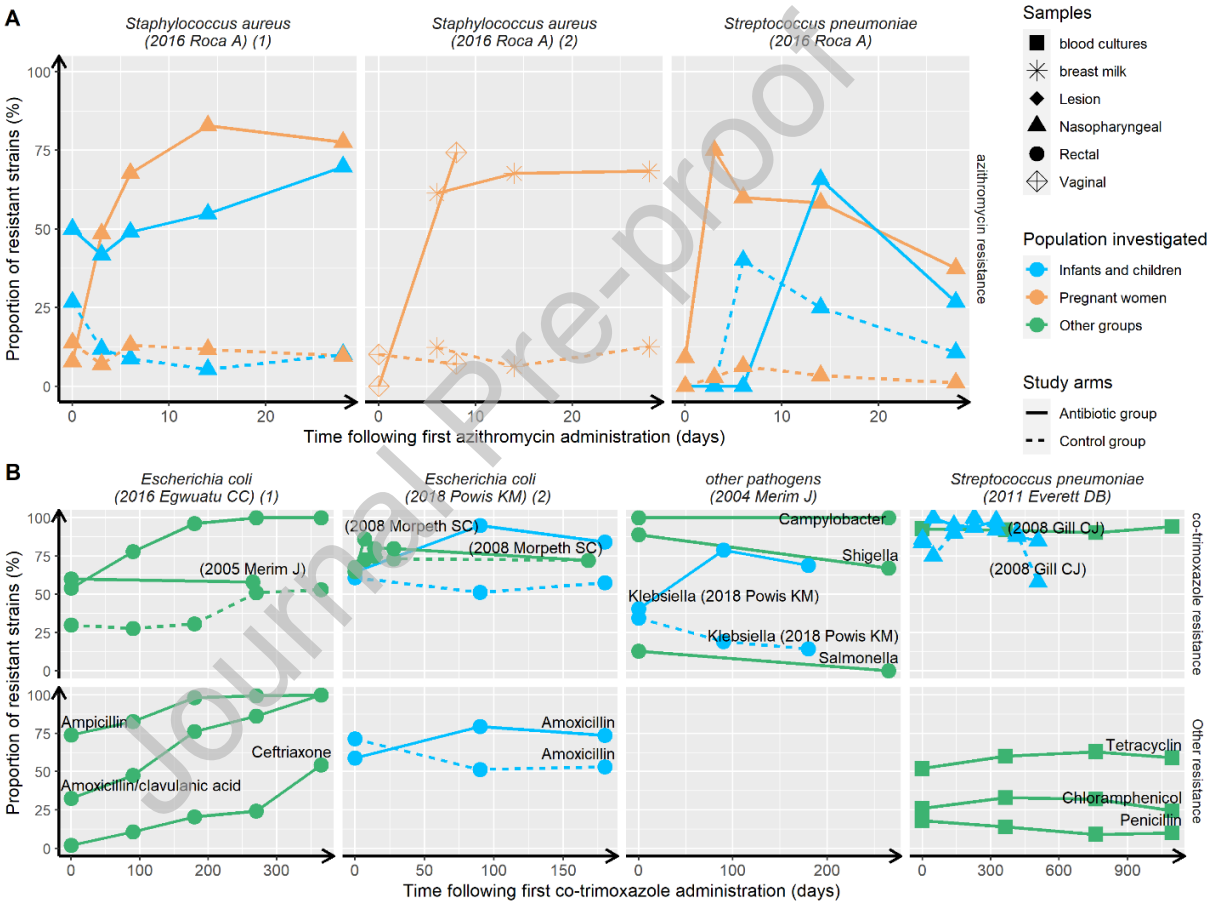
734 Legend

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736 **4A** – Resistance over time after azitromycin administration, **4B**-Resistance over time after co-trimocazole administra

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